REMARKS

In reviewing our records, it was unclear if the attachment(s) referred to in the response filed December 18, 2002 were submitted. These attachments are enclosed.

Conclusion

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 210-380 referencing docket no. 38644-170639 (formerly 378332000900). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: December 23, 2002

BY 

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21 August 2002

Dear Sirs

European Patent Application No. 98956455.4 - 2107
WALTER REED ARMY INSTITUTE OF RESEARCH
Our Ref: N.78846 GCW/JHS/cg

In response to the Article 96(2) EPC Communication dated 11 February 2002, please replace pages 9 and 58 to 61 (claims 1 to 19) with new pages 9 and 58 to 59 (claims 1 to 8) enclosed herewith. For the Examiner's benefit a copy of manuscript amended page 9 is attached.

Please also replace pages 2, 10, 20 and 21 at present on file with the manuscript amended version of these pages enclosed herewith.

Claim 1 is now directed to use of a complement inactivation inhibitor in the manufacture of a medicament for treatment of the symptoms of an immediate hypersensitivity reaction caused by an amphiphilic carrier in a pharmaceutical composition. Basis for the expression "immediate hypersensitivity reaction" can be found throughout the specification and in particular on page 2 lines 27 to 31 and page 7 lines 31 to 35.

Claim 1 defines that the pharmaceutical composition comprises an active ingredient and the amphiphilic carrier. The amphiphilic carrier is a polyethoxylated oil or a derivatized polyethoxylated oil. Basis for this can be found in claims 2 and 13 of the application as originally filed, and also in page 1 lines 24 to 25 and page 10 line 3.

The active ingredient of the pharmaceutical composition is defined as taxol, paclitaxel, althesin, cyclosporin, diazepam, didemnin E, echinomycin, propandid, a steroid, teniposide, doxorubicin, daunorubicin, amphoterin B, hemoglobin, a polynucleotide or a multivitamin. Basis for this can be found on page 9, line 29 and page 21 lines 20 to 34 and claims 6 and 17 of the application as originally filed.

Claims 2 to 5 are based on the claims in the preceding set of claims on file.

Claim 6 finds basis on e.g. page 26 lines 4 to 8.

Claim 7 is based on previous claim 14 and claim 14 as originally filed.

Claim 8 is based on previous claim 9 and claims 9 and 19 as originally filed.

The Examiner raised an objection of lack of novelty based on D1 and D2.

D1 describes an early complement activation study with a red cell substitute, a liposome encapsulated haemoglobin (LEH). The abstract of D1 states that:

> "LEH and liposomes activated human complement, as indicated by significant changes in one or more markers. The effect was primarily due to the presence of the phospholipid vehicle".

Claim 1 of the present application has been amended to define more precisely the amphiphilic carrier and the active ingredient used in the present invention. The amphiphilic carrier in claim 1 is a polyethoxylated oil or a derivatized polyethoxylated oil. This does not encompass the materials used to make the vehicle in D1.

Similar comments apply to D2 in which again a liposome-encapsulated haemoglobin was prepared. In both D1 and D2 the liposome was formed from distearoyl phosphatidyl choline/dimyristoyl phosphitadylglycerol/α-tocopherol in a 50:4.5 45:0.5 molar ratio. Neither D1 nor D2 disclose or suggest that a polyethoxylated oil such as polyethoxylated caster oil could be responsible for an immediate hypersensitivity reaction or that such a hypersensitivity reaction may be treated using a compliment inactivation inhibitor.

It is therefore considered that the claims as amended are novel over D1 and D2.

An objection of lack of inventive step was raised based on using D5 as a starting point. According to the Examination Report, the problem to be solved from D5 was how to provide an alternative formulation for inhibiting the adverse effects caused by Cremophor.

When considering identifying the problem to be solved, several Boards of Appeal decisions shed light on how the problem should be formulated. T299/85, commented:

> "However, the technical problem addressed by an invention must be so formulated as not to contain pointers to the solution, since including part of a solution offered by an invention in the statement of the problem must, when the state of the art is assessed in terms of that problem, necessarily result in an ex post facto view being taken of inventive activity."

This was confirmed in T800/91 in which the Board commented that:

> "In any case the formulated problem should be one which the skilled person would wish to solve knowing only the prior art: the problem should not be tendenciously formulated in a way that would unfairly direct development towards the claimed solution.

Although D5 acknowledges that a pharmaceutical formulation containing paclitaxel and a mixture of ethanol and Cremophor EL is known to cause hypersensitivity reactions, the abstract of D5 makes it clear that the solution envisaged is to devise a formulation "devoid of Cremophor EL". D5 is a review article which discusses some of the formulation alternatives which are considered to be most promising. All the most promising solutions to the problem of hypersensitivity reactions involved alternative formulations which omitted Cremophor EL.

Accordingly, the problem posed by D5 was how to provide an alternative formulation which omitted Cremophor EL. There is nothing in D5 to suggest to the skilled person that Cremophor EL should be retained in the composition but that further ingredients should be added in order to counteract any hypersensitivity reaction of Cremophor EL. This formulation of the problem and possible solution has been read into D5 with hindsight.

The combination of D5 with D3 and D6 and D7, possibly also D1 and D2 appears to be a combination of references which has been assembled based on hindsight. There is no common problem in these references for which the other references teach a solution. Each of D3, D6 and D7 relate to quite specific combinations of ingredients. It is not clear why these references would (not just could, but would) be combined by the skilled person, and then used in combination with D5, which explicitly recommends the removal of Cremophor EL.

It is therefore considered that the claims of the present application are inventive over the prior art.

The description has been further adapted to the revised claims.

It is believed that all of the Examiner's objections have been met. If there are any further objections please issue a written action or, if more appropriate, telephone me.

Yours faithfully

JANE H. SEXTON

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8 June 2001

Dear Sirs

European Patent Application No. 98956455.4-2107
WALTER REED ARMY INSTITUTE OF RESEARCH
Our Ref: N.78846 - DMG/JHS/lb

In response to the Article 96(2) EPC communication dated 28 September 2000, please replace pages 1, 2, 9, 16 and 24 at present on file with the manuscript amended pages enclosed herewith. Copies of these amended pages are enclosed in triplicate with the confirmation copy of this letter.

Please also replace pages 58 to 61 (claims 1 to 19) with new pages 58 to 61 (claims 1 to 19) encloses herewith. Copies of these amended pages in triplicate are enclosed with the confirmation copy of this letter. Also enclosed with the confirmation copy is a copy of the original claims showing in manuscript the amendments being made.

Claims 1 to 6, 10 and 12 to 17 have been put in second medical use format. Claims 7 to 9 and 18 to 19 now make it clear that the pharmaceutical composition comprises a complement activation inhibitor, a drug and a solvent or carrier which contains amphiphilic molecules.

The second medical use claim, claim 1, contains as a technical feature of the claim the use of a complement activation inhibitor in the manufacture of a medicament for inhibiting, treating or reducing unwanted side effects caused by a pharmaceutical composition which comprises a solvent containing amphiphilic molecules. None of the prior art documents discloses such a use. None of the prior art documents discloses or suggests that a solvent containing amphiphilic molecules causes side effects by complement activation. Similar comments apply to the other second medical use claims (claims 2 to 6; claim 10 and claims 12 to 17).

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Claims 7 to 9 and 18 to 19 are directed to pharmaceutical compositions which comprise (i) a complement activation inhibitor; (ii) a drug; and (iii) a solvent or carrier containing amphiphilic molecules. None of the prior art documents disclose a pharmaceutical composition containing this combination of ingredients.

It is therefore considered that the claims as amended are novel over the cited documents.

With respect to inventive step, the IPER sets out in Item V 3.1 an argument why claim 1 is not inventive in view of D4 in combination with D3 or D5. Essentially, the Examiner argues that D4 teaches the use of a complement activation inhibitor together with a pharmaceutical composition in order to inhibit or reduce hypersensitivity reactions, and that D3 or D5 teach that Cremophor EL (an amphiphilic molecule) causes hypersensitivity reactions. The IPER concludes that the skilled person would therefore be prompted to use the method of D4 with a solvent containing amphiphilic molecules.

However, as is explained in the introduction to the present application, despite extensive use of Cremophor EL in pharmaceuticals, there was, at the priority date, no consensus in the literature regarding whether any hypersensitivity was due to an active ingredient such as paclitaxel or to the vehicle, Cremophor EL, and how the hypersensitivity reaction is mediated (see pages 2 to 7 of the specification, particularly page 3 line 31 to page 4 line 4).

D4 is directed to concentrated injection and infusion solutions for intravascular use (D4 title). Additives are used to mitigate delayed hypersensitivity reactions (D4 page 1 lines 4 to 7). It is also stated in the description of the invention (D4 page 4 lines 17 to 19) that D4 achieves "mitigation and avoidance of delayed hypersensitivity reactions" by the addition of substances having physical or pharmaceutical effects. On page 4 lines 6 to 8 of D4 a definition is given of "delayed reactions". These are defined as those side effects that occur only one or more hours after administration of the agent in question. Thus D4 clearly teaches the skilled person that any solution proposed in D4 is addressed to the problem of delayed hypersensitivity, by which is meant reactions which only occur one or more hours after administration of the agent.

There is nothing in D3 or D5 which suggests that Cremophor EL would be regarded by the skilled person as producing a hypersensitivity reaction of the type addressed by D4. On the contrary, D3 notes on page 1402, right hand column second paragraph;

> "hypersensitivity reactions associated with Cremophor EL have historically been sporadic and rare occurrences".

D5 notes on page 89 lines 1 to 3 that;

> "studies have shown that the Cremophor EL vehicle induces histamine release and hypertension in dogs within ten minutes after administration" (emphasis added).

Thus D3 and D5 suggest that, to the extent that Cremophor EL is associated with any hypersensitivity reaction, this is not a delayed reaction. Accordingly, the skilled person would not consider the teachings of D3 or D5 to be relevant to the problem addressed by D4. The skilled person is not therefore taught by the prior art that amphiphilic molecules produce a hypersensitivity which is mediated by complement activation. There is no suggestion in the prior art that a complement activation inhibitor could or should be used to inhibit, treat or reduce unwanted side effects caused by a pharmaceutical composition which includes a solvent or carrier amphiphilic molecules.

It is therefore considered that claim 1 is inventive over the prior art.

For similar reasons, the skilled person is not taught by the prior art to combine the elements of a complement activation inhibitor, a drug and a solvent or carrier containing amphiphilic molecules in a single pharmaceutical composition in the expectation that the resulting composition would produce reduced side effects resulting from the presence of the amphiphilic molecules.

For similar reasons the method of claim 11 is inventive over the prior art. In the absence of any prior art teaching which suggests that hypersensitivity can result from the use of a carrier or solvent comprising amphiphilic molecules and that this is mediated by complement activation, the skilled person would not devise or carry out a method in accordance with claim 11, in which hypersensitivity reactions are predicted by incubating a drug composition containing polyethoxylated oil and detecting the presence or absence of complement activation.

It is therefore considered that the claims as amended are inventive over the prior art.

In response to Item VIII of the IPER the pharmaceutical composition claims have been amended so that they are now clear in scope.

The Examiner also objected to the terms "Cremophor" and "Cremophor EL" in claim 4. It is believed that these terms are clear in scope. A definition of these terms has been included in the description (page 20 lines 20 to 31). The incorporation of this passage into claim 4 would render it lacking in conciseness (contrary to Article 84). It is believed that the most appropriate wording which meets the requirements of Article 84 is to refer to Cremophor.

The term "taxol" has been amended to refer to drug by its generic name, paclitaxel.

The description has been adapted to the revised claims to make it clear that a method of treatment *per se* is not being claimed. It is believed that all the Examiner's objections have been met. If there are any further objections, please issue a written action or, if more appropriate, telephone me. Merely as a precaution, in the event that the Examiner is contemplating refusing the application without allowing the applicant an opportunity for further amendment or

comment, Oral Proceedings are requested.

Please acknowledge receipt of the confirmation copy of this letter by dating and returning the attached copy.

Yours faithfully

JANE H. SEXTON